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MZ Female Twins Discordant For X-Linked Diseases: A Review

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Abstract. The 20 reported cases of MZ female twins discordant for X-linked diseases are reviewed. In such twins the X-inactivation pattern is opposite skewing (abnormal allele inactivated in most cells of the normal twin, and normal allele inactivated in most cells of the affected twin) or skewing in one twin and random in the cotwin. The diseases involved map in two specific regions: Xq27-28 and Xp21. The only exceptions are Fabry's disease and Aicardi's syndrome, which map in Xq22 and Xp22 respectively. No concordant MZ female carrier twins, either normal or affected, have been described. Three main hypotheses have been proposed to explain such characteristics [2, 5, 14], but none is completely satisfactory. The constant discordance for X-linked diseases in MZ female twins has important consequences for genetic counselling.

Key words: MZ twins, X-linked recessive diseases, Discordance in MZ twins

INTRODUCTION

In 1912 the first case of MZ twins discordant for an X-linked disease, the colour-vision deficiency was reported [15]. Since then, another 19 pairs of MZ female twins discordant for X-linked diseases have been described: four pairs discordant for colour-vision deficiency [7, 9, 18, 22]; two for haemophilia B [8, 19]; one for G6PD deficiency [17]; seven for Duchenne Muscular Dystrophy (DMD) [1, 2, 3, 6, 12, 16, 21, 28]; two for fragile-X [10, 24]; one for Aicardi's syndrome [4]; one for Hunter's syndrome [27], and one for Fabry's disease [13].

The most relevant features of such twins are the following.

1) Normal karyotype.

2) One twin is always severely affected, while the cotwin is completely normal. Intermediate phenotypes have not been reported.

3) The X-inactivation pattern is opposite skewing (abnormal allele inactivated in

most cells of the normal twin, and normal allele inactivated in most cells of the affected twin) or skewing in one twin and random in the cotwin.

4) The diseases involved map in two specific regions: Xq27-28 (colour vision deficiency, haemophilia B, G6PD deficiency, fragile-X, and Hunter's syndrome) and Xp21 (DMD). The only exceptions are Fabry's disease and Aicardi's syndrome, which map in Xq22 and Xp22 respectively.

No concordant female carrier twins, either normal or affected, have been described. Three main hypotheses have been proposed to explain such characteristics:

1) casual aggregation of cells carrying the same inactivated chromosome predisposes to twinning [2];

2) a 'sampling effect' through early symmetric or asymmetric splitting of the inner cell mass occurring after X-inactivation [14];

3) early mitotic crossing over, segregation of one crossed and one uncrossed chromatid in the daughter cells, and obligatory inactivation of the uncrossed chromatid [5].

We reviewed the literature relating to the reported cases of MZ female twins discordant for X-linked diseases, and discuss here the foregoing hypotheses and their consequences for genetic counselling.

REPORTED CASES

The discordant twins reported hitherto are shown in the Table. Zygosity determination cannot be considered reliable in the first three cases of colour-vision deficiency [15, 22, 25]. Obviously, in these cases cytogenetic analysis was not performed either.

Table - MZ female twins discordant for X-linked diseases

Disease	Lyonization	Locus	Reference
Color vision deficiency	—	Xq28	[15]
Color vision deficiency	—	Xq28	[22]
Color vision deficiency	—	Xq28	[25]
Color vision deficiency	—	Xq28	[9]
Color vision deficiency	opposite skewing in fibroblasts; random in both twins in lymphocytes	Xq28	[7], [18]
Hemophilia B	—	Xq27.1–27.2	[19]
Hemophilia B	—	Xq27.1–27.2	[8]
G6PD deficiency	—	Xq28	[17]
Fragile X	Opposite skewing in lymphocytes	Xq27.3	[24]
Fragile X	Opposite skewing in lymphocytes	Xq27.3	[10]
DMD	—	Xp21.2	[6]
DMD	Opposite skewing in fibroblastes	Xp21.2	[2]

Table - Continued

Disease	Lyonization	Locus	Reference
DMD	—	Xp21.2	[3]
DMD	—	Xp21.2	[16]
DMD	Opposite skewing in fibroblasts and lymphocytes	Xp21.2	[21], [28]
DMD	Skewed in the affected twin, random in the normal twin in lymphocytes	Xp21.2	[12]
DMD	Opposite skewing in fibroblasts and lymphocytes	Xp21.2	[1]
Hunter's syndrome	Skewed in the affected twin, random in the normal twin, in fibroblasts and lymphocytes	Xq28	[27]
Fabry's disease	—	Xq22	[13]
Aicardi's syndrome	Random in both twins' lymphocytes	Xp22	[4]

In all the other twins, karyotype and zygosity analyses using blood, HLA or VNTR polymorphisms were carried out. In nine couples, X-inactivation studies were performed and showed: opposite skewing inactivation in six cases [1, 2, 7, 10, 28]; skewing inactivation in the affected twin and random inactivation in the normal twin in two cases [12, 27]; and random inactivation in both twins in one case [4]. However, exchange of hematopoietic tissue due to prenatal vascular anastomosis may alter the X-inactivation pattern in lymphocytes. Indeed, in the couple described by one study [7], the inactivation was random in both twins in lymphocytes but opposite skewing in fibroblasts.

We cannot exclude the possibility that a similar pattern might also have been found in the case of Aicardi's syndrome described [4], if fibroblasts had also been studied. However, of the 20 diseases listed, Aicardi's syndrome is the only one with X-linked dominant transmission. In such cases, the disease could have been caused by a neomutation occurring in one twin only during early embryonic development [4]. Indeed, in X-linked dominant conditions, the disease also occurs with random lyonization.

DISCUSSION

Hypothesis 1 - Casual aggregation of cells carrying the same inactivated chromosome predisposes to twinning [2].

As shown in Fig. 1, by pure chance, all the cells containing the inactivated normal allele may cluster on one side of the inner cell mass, and all the cells containing the inactivated normal allele cluster on the other side. This particular aggregation would predispose to

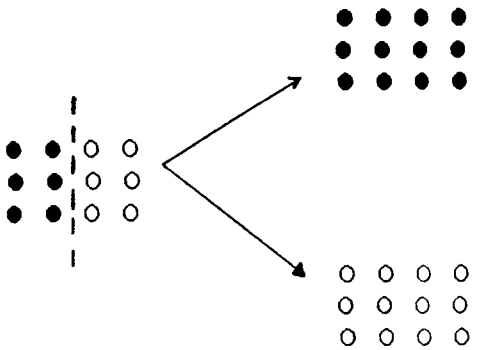

Fig. 1. Burn's hypothesis: casual aggregation of cells carrying the same inactive X-chromosome predisposes to twinning.

MZ twinning. The opposite skewing inactivation reported in most of the pairs and the absence of concordant twins are easily explained by this theory. On the other hand, the existence of couples with random inactivation in one twin and skewing in the other does not fit with this hypothesis. Moreover, if clustering of cells with the same inactivated X- chromosome predisposes to twinning, there should be an excess of MZ female twins and of normal MZ female twins with skewing inactivation. Yet neither of these features has been reported. However, the two studies of inactivation in normal twins were only performed on lymphocytes [19, 26].

Hypothesis 2 - A 'sampling effect' through an early symmetric or asymmetric splitting of the inner cell mass occurring after X-inactivation [14].

A symmetric splitting of the inner cell mass occurring after lyonization could produce by pure chance, either opposite-skewing discordant twins (Fig. 2a) or normal concordant twins, both with random lyonization (Fig. 2b). An asymmetric splitting might more often lead to a random lyonization in the normal twin and skewing in the affected cotwin (Fig. 2d). According to this theory, the occurrence of affected concordant twins would be extremely rare, since most of the cells of the inner cell mass should contain the inactivated normal allele (Fig. 2c), which is improbable. Indeed, affected concordant twins have not been described in the literature. On the other hand, normal concordant twins, both with random lyonization (Fig. 2b) should occur frequently. However, no instance of normal concordant heterozygous twins has been reported.

Hypothesis 3 - Early mitotic crossing over, segregation of one crossed and one uncrossed chromatid in the daughter cells, and obligatory inactivation of the uncrossed chromatid [5].

Mitotic crossing over in man is not a rare occurrence [23]. As shown in Fig. 3, daughter cells could receive one crossed and one uncrossed chromatid. If we assume that the the uncrossed chromatid is always inactivated, one cell would express the abnormal and the other the normal allele. If twinning were to occur at the two-cell stage, the twins would

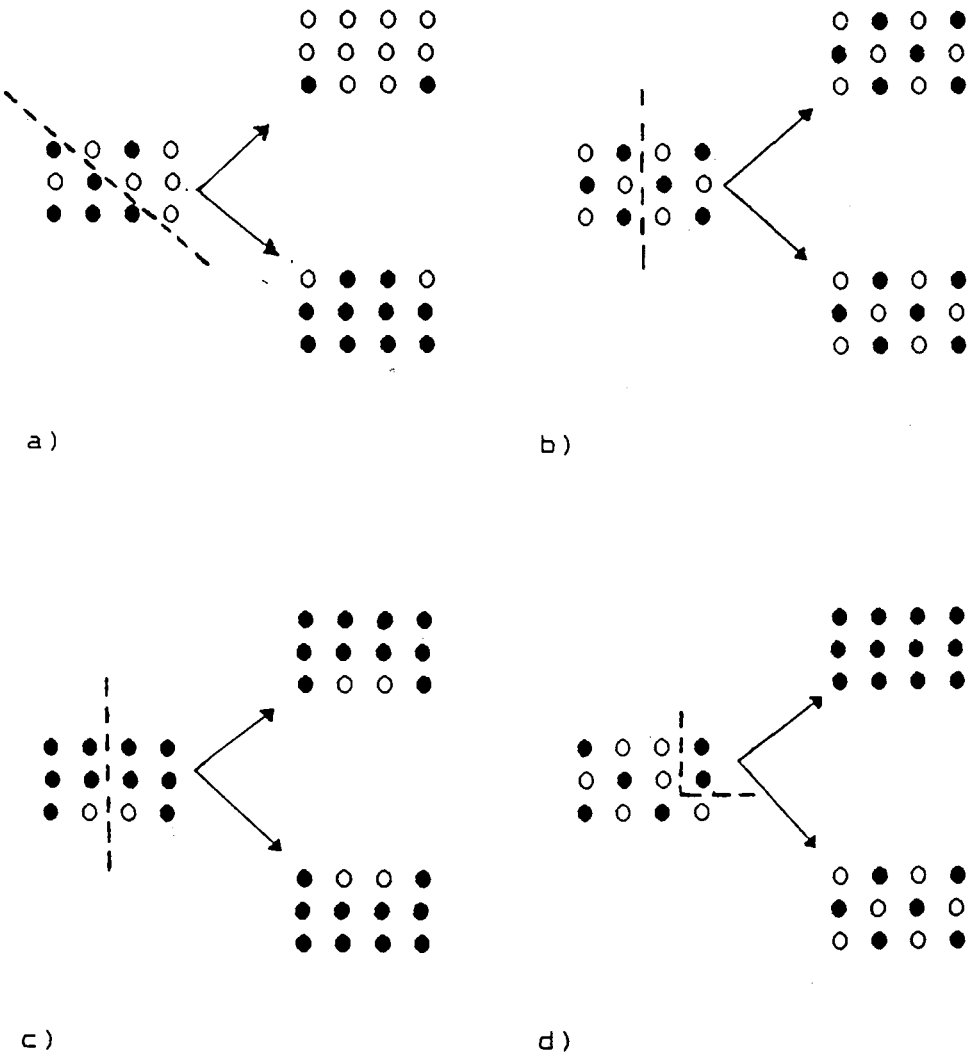

Fig. 2. Nance's hypothesis: symmetrical splitting of the inner-cell mass (a, b, c) can lead, by chance, to opposite skewing (a) or random lyonization in both twins (b). Concordant affected twins could occur very rarely, since most cells of the inner-cell mass should carry the inactivated normal allele (c). Asymmetric spliting of the inner-cell mass (d) can more probably lead to a random lyonization in one twin and skewing in the other.

Legends to Figs. 1 and 2

● = cells carrying the inactivated normal allele.
○ = cells carrying the inactivated abnormal allele.
– – – – = splitting direction.
To the left: unsplit embryo
To the right: twin embryos

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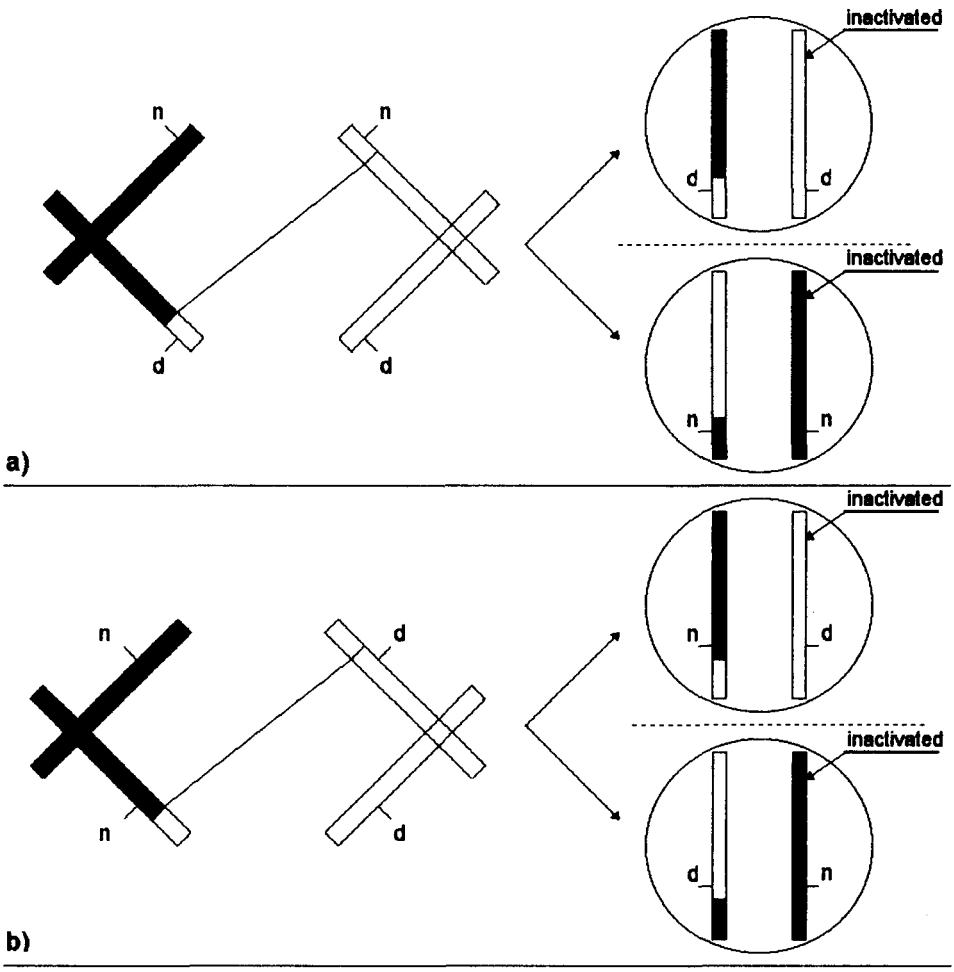

Fig. 3. Cotè's hypothesis: early mitotic crossing-over, segregation of one crossed and one uncrossed chromatid in the daughter cells, and obligatory inactivation of the uncrossed chromatid always produce opposite skewing inactivation and discordant twins. Since loss of heterozygosity has not been reported, crossing over distal to the disease-gene (b) is more likely than proximal crossing over (a).

Legend to Fig. 3:

d = disease-gene
n = normal gene
--- = splitting direction

invariably be opposite-skewing and discordant. In addition, discordance due to mitotic crossing-over is expected to be more frequent for diseases which map in the distal chromosomal regions, such as Xq27-28 and in such exchange-prone regions as Xp21. However, if crossing-over were to occur proximally to the region concerned, a loss of heterozygosity would result (Fig. 3a). This has not been observed. A crossing-over distal

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to the disease-gene (Fig. 3b) could also produce opposite skewing, and discordant twins, without loss of heterozygosity in the region containing the gene, but in this case, the high frequence of discordance for disease mapping in the distal regions of the X chromosome would remain unexplained. Moreover, this theory cannot explain the finding of random inactivation in one twin and skewing in the other.

CONCLUSIONS

None of three hypotheses proposed can completely explain the characteristics of discordant MZ female twins for X-linked diseases. However, the peculiar pattern of lyonization in discordant twins and the absence of concordant affected or concordant normal twins suggest that twinning and lyonization are two interrelated events. An intriguing relation between lyonization, twinning and imprinting is suggested by the fact that MZ twins discordant for Beckwith-Wiedmann syndrome, an autosomal dominant 'imprintable' syndrome, are invariably female [11]. Nonetheless, the exact mechanism which links lyonization, twinning and imprinting remains puzzling. The constant discordance for X-linked diseases in MZ female twins has important consequences for genetic counselling. In the occurrence of a couple of heterozygous MZ female twins, there is a very high probability that one of the twins will be affected. Moreover, a sizeable proportion of twin pregnancies result in a singleton only, since one of the twins often dies very early in pregnancy. If an early scan has not been performed, we cannot be sure that a singleton is not the survivor of a twin pregnancy, in which case the probability of his being affected will be very high. Inactivation studies even in singleton heterozygote females would be advisable, especially if an early scan has not excluded loss of a twin.

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